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## Desolvation and substituent effects in edge-to-face aromatic interactions\*\*

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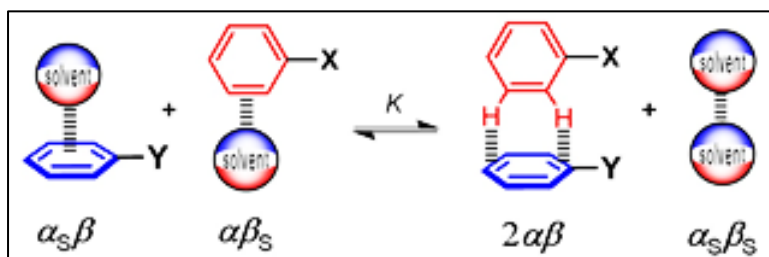
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### Supporting information:

Electronic supplementary information (ESI) available: Details of the calculation of H-bond parameters and comparative plots for both DFT and AM1 electrostatic potentials. See <http://dx.doi.org/10.1039/B902351H>

### Graphical abstract:



### Summary:

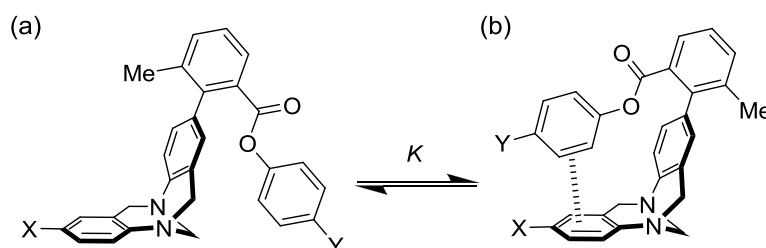
The electrostatic solvent competition model accounts for the thermodynamic properties of aromatic interactions in supramolecular systems, when edge-to-face contacts are considered as two point CH- $\pi$  hydrogen bonding interactions.

## Abstract

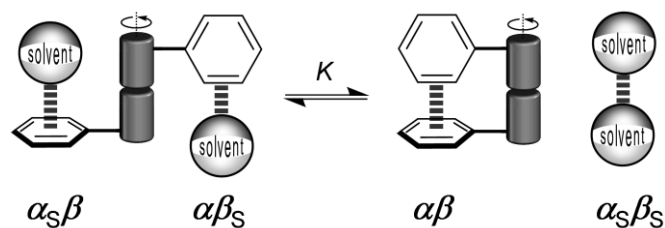
Fresh experimental data reveals that aromatic edge-to-face interaction energies measured in both molecular torsion balances and supramolecular zipper complexes can be predicted using a simple solvation model and  $\alpha/\beta$  H-bond constants.

## Introduction

Supramolecular systems provide the ideal testing ground for the development of theoretical models for intermolecular interactions and molecular recognition processes in general.<sup>1</sup> Structurally well-defined chemical systems allow the relationship between chemical structure and the thermodynamics of non-covalent interactions to be systematically explored, facilitating the design of experiments that test specific aspects of theoretical and computational models. In principle, it is possible to compute the properties of molecular systems from first principles using quantum mechanics *ab initio*. However in practice, this remains a challenging problem, because the free energy changes associated with non-covalent interactions are of the order of a few  $\text{kJ mol}^{-1}$ , and so the enthalpy and entropy contributions for a conformational ensemble of solvated molecules must be calculated to a level of accuracy that is difficult to achieve routinely. In favourable cases, where computational methods are successful, the calculation provides a description of the system as a whole, and it is difficult to dissect out the individual factors that govern the observed behaviour. The interplay of collectively optimised variables complicates the partitioning of individual energetic contributions to reliably separate cause and effect. Therefore, more approximate empirical descriptions of the relationship between chemical structure and molecular interactions continue to provide valuable tools to guide the supramolecular design process. The molecular torsion balance designed by Wilcox is one of the most elegant examples of a supramolecular scaffold for probing structure-activity relationships in aromatic interactions (Figureure 1).<sup>2-5</sup> We recently proposed a simple model that accounted for the variation in the results obtained for different torsion balance systems.<sup>6</sup> The ideas are summarised Figureure 2.



**Figure 1.** The ‘molecular torsion balance’ developed by Wilcox for the quantification of aromatic interactions (a) the unfolded (free) state (b) the folded (bound) state which contains an additional edge-to-face aromatic interaction.



**Figure 2.** Generic folding equilibrium for a molecular torsion balance including the solvent. The position of equilibrium is determined by four free energy contributions: i)  $\alpha_s\beta$  - the interaction between the aromatic face and the solvent; ii)  $\alpha\beta_s$  - the interaction between the edge of the aromatic ring and solvent; iii)  $\alpha\beta$  - the edge-to-face aromatic interaction; and iv)  $\alpha_s\beta_s$  - the interaction between displaced solvent molecules.

The observed free energy difference between the two conformational states of the molecule is determined by the competition between the edge-to-face aromatic interaction in the folded state and the solvation interactions in the open state. The trends in the aromatic interaction energies observed in this system can be understood using the electrostatic solvent competition model that we introduced for understanding solvent effects on H-bonding interactions.<sup>7</sup> Specifically, Equation 1 allows accurate prediction of how both the solvent and the aromatic substituents affect the equilibrium position of the torsion balance.

$$\Delta\Delta G = -(\alpha - \alpha_s)(\beta - \beta_s) \quad \text{Equ. (1)}$$

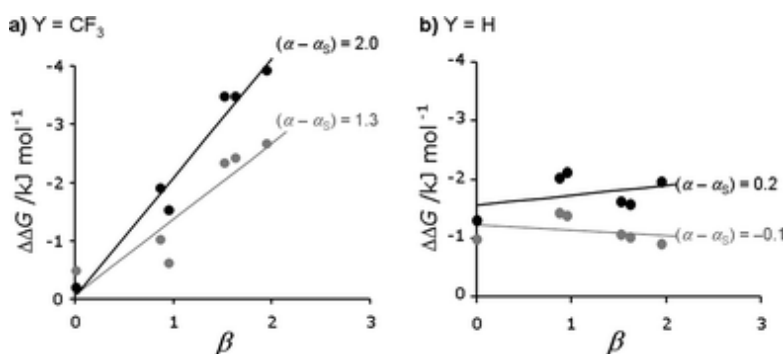
where  $\alpha$  and  $\beta$  are H-bond parameters for the edge and face ring,  $\alpha_s$  and  $\beta_s$  are the corresponding parameters for the solvent. In the system discussed previously,<sup>[6]</sup> aromatic interactions were measured as a function of face ring substituent, so Equation 1 can be reduced to:

$$\Delta\Delta G = -(\alpha - \alpha_s)\beta + c \quad \text{Equ. (2)}$$

The experimental studies have recently been expanded by the Diederich group, so that we now have a complete picture for both types of torsion balance in both  $C_6D_6$  and  $CDCl_3$ .<sup>5</sup> Detailed *ab initio* calculations that partition the computed energy into different contributions suggest that the experimental behaviour is dominated by dispersion phenomena.<sup>8</sup> Nevertheless, the new experimental results are also in excellent agreement with Equation 2, which is based solely on electrostatic arguments (Figureure 3).

Y	solvent	theory	experiment
CF <sub>3</sub>	benzene	1.6	2.0
CF <sub>3</sub>	chloroform	1.4	1.3
H	benzene	0.0	0.2
H	chloroform	-0.2	-0.1

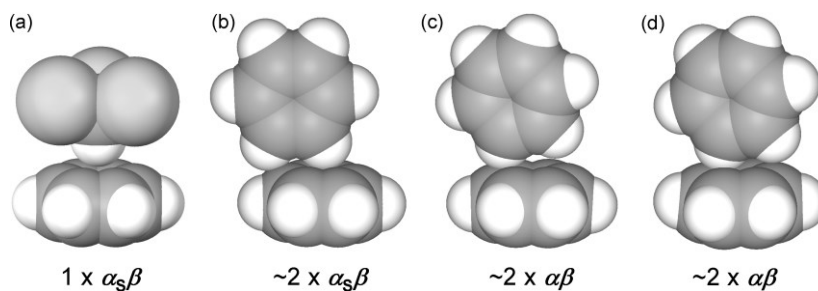
**Table 1.** Values of  $(\alpha - \alpha_s)$  from Equation 2 (theory) and from the slopes of the best fit straight lines in Figureure 3 (experiment).



**Figure 3.** Experimental folding free energies for molecular torsion balances plotted as a function of the H-bond acceptor constants ( $\beta$ ) of the aromatic face for various X-substituents. (a)  $Y = CF_3$  (b)  $Y = H$  in  $C_6D_6$  (black) and  $CDCl_3$  (grey). H-bond parameters from DFT/6-31G\* calculations (see ESI for details and the AM1 version of this plot).

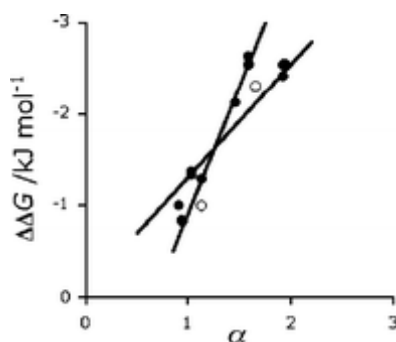
The key point for understanding aromatic interactions in the torsion balance system relates to the properties of the solvents. Chloroform ( $\alpha_s = 2.2$ ) is more polar than benzene ( $\alpha_s = 1.0$ ), so the electrostatics of the edge-to-face interaction should be damped in chloroform. However as we pointed out previously,<sup>[6]</sup> the torsion balance behaviour can be rationalised in a quantitative way by considering an important fundamental difference between aromatic-aromatic interactions and aromatic-chloroform interactions. Specifically, chloroform can make only one H-bond to the face of an aromatic ring, due to its steric bulk, whereas an aromatic ring makes two CH- $\pi$  contacts with the face of an aromatic ring.

These intermolecular interaction motifs are indeed observed in structures from X-ray and neutron diffraction studies (Figure 4). Thus the  $\alpha$  parameter that must be used in Equation 1 for an aromatic CH H-bond donor is double the value for a conventional H-bond interaction at a single site on the edge of the aromatic ring. This is the model that accounted quantitatively for the trends discussed in our previous paper: for the  $CF_3$  edge ring,  $\alpha = 2 \times 1.8$ ; for the unfunctionalised edge ring,  $\alpha = 2 \times 1.0$ ; for the benzene solvent,  $\alpha_s = 2 \times 1.0$ ; for the chloroform solvent,  $\alpha_s = 1 \times 2.2$ .<sup>6</sup>



**Figure 4.** Aromatic interaction motifs determined by X-ray and neutron diffraction studies. a) aromatic solvation by chloroform<sup>9</sup> b) aromatic solvation by benzene (CCDC no. BENZEN01).<sup>10</sup> c) the aromatic edge-

to-face interaction in a folded torsion balance ( $Y = \text{NO}_2$ ,  $X = \text{Me}$ , CCDC no. PIWYEZ)<sup>2</sup> and d) in a model compound of the supramolecular zipper complexes (Figure 6,  $Y = t\text{-Bu}$ ,  $X = \text{NMe}_2$ , CCDC no. ACANAT). Aromatic substituents in a), c) and d) omitted for clarity.



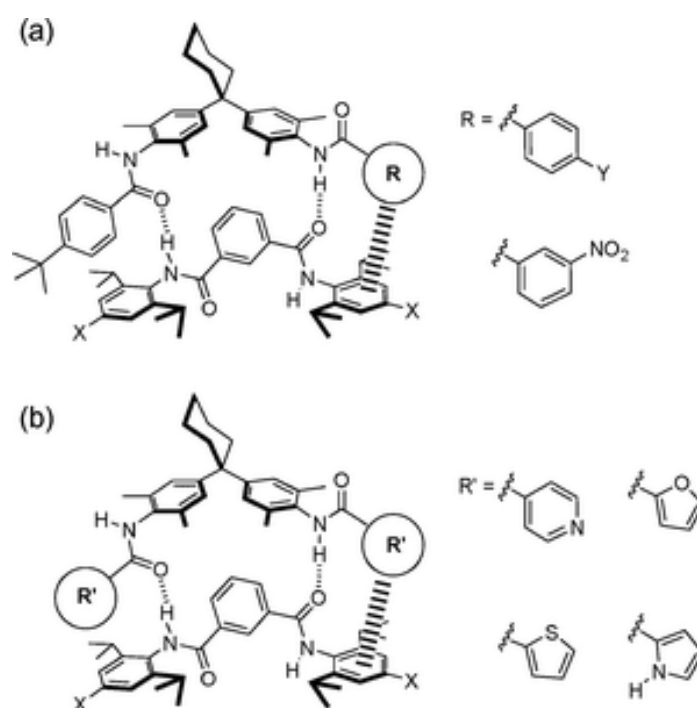
**Figure 5.** Experimental folding free energies for molecular torsion balances where  $X = \text{Me}$  (black) and  $X = \text{H}$  (unfilled circles) in  $\text{CDCl}_3$  (grey) versus the H-bond donor constants ( $\alpha$ ) of the aromatic edge protons for various  $Y$ -substituents. H-bond parameters from DFT/6-31G\* calculations (see ESI for details and the AM1 version of this plot). The electrostatic surface potentials of the aromatic face are almost identical for  $X = \text{H}$  and  $\text{Me}$ .

This model makes an excellent prediction of the behaviour described in the new work reported by Diederich (Table 1, Figure 3). In effect, chloroform is only marginally more polar than benzene with respect to aromatic interactions, but the  $\text{CF}_3$ -substituted edge ring is significantly more polar than the unfunctionalised edge ring. Thus large electrostatic effects are observed for the  $\text{CF}_3$  edge ring interactions, because the combined effect of the two aromatic CHs is significantly more polar than either chloroform or benzene ( $\alpha = 3.6$  versus  $\alpha_s = 2.2$  or  $2.0$ ). The substituent effects are attenuated slightly on changing the solvent from benzene to chloroform, but the effects are not large because the change in  $\alpha_s$  is small ( $2.0$  compared with  $2.2$ ). For the unfunctionalised edge ring,  $\alpha$  and  $\alpha_s$  are similar in all cases, and so substituent effects are small in both solvents. Although, there is some scatter in Figure 3, the agreement between the predicted and experimentally observed trends is clear (minor discrepancies may come from interactions involving the ring substituents that are not accounted for in this simple first-order model).

It is possible to gain some insight into the influence of the edge ring substituent on the torsion balance folding free energy by collating experimental measurements made by Wilcox, Ren, and Diederich in  $\text{CDCl}_3$  where the face ring substituent is constant,  $X = \text{Me}$  or  $\text{H}$ .<sup>2, 4, 5</sup> In this case, the electrostatic solvent competition model is reformulated as Equation 3.

$$\Delta\Delta G = -(\beta - \beta_s) \alpha + c \text{ Equ. (3)}$$

Figure 5 shows that the torsion balance folding free energy does indeed correlate with the H-bond constant of the edge ring,  $\alpha$ . The strong substituent effect on the aromatic interaction in this system arises because  $\text{CDCl}_3$  is a weak H-bond acceptor ( $\beta_s = 0.8$ ) that does not compete well with the aromatic face ( $\beta = 2.2$ ). Although the overall trend is clear, the data in Figure 5 come from different laboratories, and the variation in  $\alpha$  is small, hampering a quantitative interpretation of the slope (values between 1.2 and 2.8 are consistent with the data as illustrated, with a best fit value of 1.6). Assuming two CH- $\pi$  interactions as before, the prediction of Equation 3 is a slope of  $2(\beta - \beta_s) = 2.8$ .



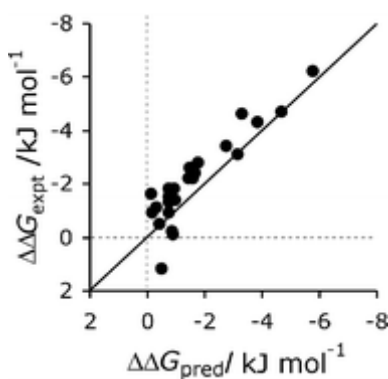
**Figure 6.** Supramolecular zipper complexes used in combination with the double-mutant cycle approach for quantifying edge-to-face aromatic interactions for various combinations of X and Y ( $\text{NMe}_2$ , H and  $\text{NO}_2$ ).

The double H-bond hypothesis for the edge-to-face aromatic interaction illustrated in Figure 3 has implications for understanding structure-activity relationships in other systems. For example, we can now apply this model to the intermolecular aromatic interactions that we have measured using the double mutant cycle approach in chloroform (Figure 6).<sup>11</sup> Both the  $^1\text{H}$  NMR solution structures of these zipper complexes and the crystal structures of model compounds revealed two CH- $\pi$  interactions. The free energy of the edge-to-face interactions in this system is given by Equation 4 where the value of  $\alpha$  for the edge ring is multiplied by a factor of two to account for the two CH- $\pi$  interactions that are made with

the face ring in the bound state and the two solvent interactions that are made in the free state. The factor of 1.5 accounts for the solvation of the three solvent molecules liberated upon complexation.

$$\Delta\Delta G = -2\alpha\beta + 2\alpha\beta_s + \alpha_s\beta - 1.5\alpha_s\beta_s \text{ Equ. (4)}$$

The predictions of Equation 4 agree remarkably well with the experimental measurements of edge-to-face aromatic interactions reported previously (Figure 7 and supporting information Table S3). The quality of the correlation is particularly good for attractive interactions, but where the interaction energy is less favourable (interactions with the face of a nitroaromatic) the data are more scattered, because alternative conformations and substituent interactions contribute to the observed interaction energies.



**Figure 7.** Comparison of experimental ( $\Delta\Delta G_{\text{expt}}$ ) and predicted ( $\Delta\Delta G_{\text{pred}}$ ) edge-to-face aromatic interaction energies in supramolecular zipper complexes in  $\text{CDCl}_3$ .  $\alpha/\beta$  values used in Equation 3 from DFT/6-31G\* calculations (see ESI for details and the AM1 version of this plot).

The analysis presented here indicates that electrostatic effects play a dominant role in determining the properties of aromatic interactions in organic solvents. The electrostatic solvent competition model that we introduced previously for H-bonding interactions can be applied equally well to aromatic interactions. However, the delicate balance of desolvation and functional group interactions is critical in these weaker non-covalent interactions and gives rise to remarkably different behaviour for closely related systems. The experimental results suggest that edge-to-face aromatic interactions involve two point H-bonding between the two CH donors of the edge ring and the  $\pi$ -electron density of the face ring. This allows the aromatic CH H-bond donor to compete with the more polar CH donor of chloroform which can only make a single point interaction, that sterically occludes the whole of the face of the  $\pi$ -system. This analysis has allowed us to rationalise a wide range of data on aromatic interactions in torsion balances and supramolecular zipper complexes, providing a simple account of the interplay between solvent effects and substituents on both the edge and the face ring.



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